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Current UK practices on Health Economics Analysis Plans (HEAPs): Are we using heaps of them?

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Background

Economic evaluation has increasingly become an integral component of Randomised Controlled Trial (RCT) designs. UK organisations, such as the National Institute for Health Research's Health Technology Assessment (NIHR HTA) Programme and the Medical Research Council, fund RCTs that try to address both clinical effectiveness issues as well as cost-effectiveness considerations. The proposed economic evaluation is outlined in the application, and once a proposal is funded, a section in the protocol may describe the intended analysis to be followed as part of the economic evaluation based on the RCT. Guidance on how to conduct economic evaluation alongside RCTs has been published elsewhere [1] together with considerations around methodological issues and the novel approaches that may be applied [2].

A guidance document (known as a Standard Operating Procedure) that outlines the predetermined steps and instructions to be followed as part of the economic as well as the statistical analysis of a trial is an important aspect of the quality management of any trial. In a way, it safeguards the transparency and consistency of the higher level steps that should be followed as part of any analysis.

However, little is known to date about how to integrate health economics operating procedures, and health economics analysis plans (HEAPs) as part of a study. Common questions arising are i) Is a HEAP always needed? ii) What information should be included as standard? iii) Can a proposed HEAP be changed, and if so, in what circumstances?

Before answering these very important questions, we took a step back to first identify current practice and opinions about the use of HEAPs and HEAP Standard Operating Procedures (SOPs). We expected a-priori that Clinical Trials Units (CTUs) and individual health economists would follow specific instructions about who should write and approve a HEAP, for whom, and when as well as the types of RCTs for which a HEAP is necessary.

Methods

Six health economists and one statistician from the Universities of Oxford, Warwick and Bristol, under the umbrella of the MRC Network of Hubs for Trials Methodology Research, were involved in the design of an electronic survey targeting registered UK Clinical Trial Units (http://www.ukcrc-ctu.org.uk/).

For the purpose of the survey a HEAP was defined as: "*a document which provides details on the economic analysis to be followed as part of a trial. The final report and any subsequent analysis should follow the main principles outlined in the HEAP. Any deviations from the HEAP should be described and justified in the final report of the trial*". A HEAP Standard Operating Procedure (SOP): "*describes the procedure for the development and utilisation of a HEAP for Clinical Research. The SOP does not address the use of specific health economics procedures or methods, but rather outlines all important details of the design and conduct of the clinical research and the principle features of its proposed economic analysis, to avoid post-hoc decisions that may affect the credibility and interpretation of the economic analysis*". Both definitions were discussed with all individuals involved in the design of the survey with disagreements resolved through consensus.

The survey was tested amongst health economists, clinicians and statisticians, with a few changes made to improve stratification of some of the available replies, before being expanded to the full set

of CTUs with the web-based survey link live for two months (April/May 2017). Health economists named as collaborators with CTUs were identified though each CTU's website, and were the primary target group for the survey. If health economists were not identified, then the lead statistician was contacted and if no health economist or statisticians were named on the CTU website, then the CTU director was approached. Study participants were recruited by email.

The survey asked for each participant's name, the CTU or organisation they belonged to and their job title, and was therefore not anonymous. Participants were asked among other questions if they had a health economics team embedded (i.e. employed staff) within their CTU, if the RCTs run by the CTU had HEAPs and if their CTU had a HEAP SOP or instructions in place (the detailed questionnaire can be found in the Appendix). None of the questions were mandatory.

Results

From the original 46 UK fully registered CTUs contacted, six CTUs identified a common health economist (three pairs of CTUs employing the same health economist) and another four did not have available contact information.

From the 39 remaining CTUs our response rate was 72% (28/39). The majority of respondents were health economists (71%), followed by statisticians (21%) and heads of operations or co-directors (4%), respectively. Table 1 presents details of responses to each survey question.

Only 39 % (11/28) of the respondents reported a health economics team embedded within their CTUs, 29% do not have health economics teams embedded within their units, but work closely with external health economics teams, and a further 32% employed other arrangements. In terms of HEAPs and HEAP SOPs, our survey suggests that one third of CTUs **always** have a HEAP in place, whereas only 37 % of them have HEAP SOPs or broader instructions in place. In terms of type of study, full RCTs and publicly funded RCTs were more likely to **always** have a HEAP (57% and 43%, respectively). Health economists, regardless of seniority level, were the major contributors to drafting a HEAP, as expected. Study chief investigators were less involved (52%) in writing up the HEAP, and statisticians were the least likely to be the main contributors (19%). In terms of HEAP approval and signing off, the chief investigator and the internal senior health economist were the main contributors. When we asked participants to state from the selected options for whom they think a HEAP is written, with multiple responses permitted, the largest proportion selected health economists (93%), followed by the chief investigator (85%), Trial Management Group members and Trial Steering Committee members (74% respectively), the chief statistician (70%), the funder (59%), Data Monitoring and Ethics Committee members (48%) and others (7%). Finally, with regards to the best time to produce a HEAP, more than one half of the participants (54%) agreed it should be any time before the database is locked and final analysis begins.

Discussion

As the number of clinical trials with health economic endpoints continues to grow, a standardised approach towards analysis and reporting of results [3] becomes imperative for ensuring transparency and replicability of the results [4].

A proposal to standardise operating procedure for HEAPs was published back in 2008 by a team of health economists at Bangor University [5]. Our survey suggests that only one third of the UK based

CTUs have HEAP instructions in place, and that these are largely for internal use only. Around 30% of CTUs write HEAPs as a standard practice. The lack of consistency concerning the people who are involved in writing up and signing off the analysis plan, the intended audience and the timing of writing a HEAP, all contribute to an inconsistent approach towards HEAPs.

A potential limitation of our survey is the variability in the interpretation of our findings with respect to the definition of some of the predefined categories. More specifically, "always" is interpreted as 100% of the time, whereas "sometimes" could range from 1-99% of the times. That makes it difficult for some of the survey answers to be strictly quantifiable.

Conclusion

Owing to respondents' lack of consensus about their own approach or their unit's approach towards economic analysis within RCTs, we suggest that all registered UK CTUs would benefit from guidelines and instructions for the development of HEAPs and HEAP SOPs. A systematic and transparent approach should be followed to develop Health Economic Analysis Plans to complement trial protocols, which should enhance the reproducibility of the data analysis and also the overall quality management of the trial.

Abbreviations

HEAP: Health Economics Analysis Plan; SOP: Standard Operating Procedure; RCT: Randomised Controlled Trial

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The concept of this paper was conceived by MD. All authors assisted in designing the survey and critically appraise the manuscript. All authors read and approved the final manuscript.

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Table 1. Survey results (n=28)

Question		Frequency	%
Do you have a health economics team embedded within your CTU?	Yes	11	39.29
	No	8	28.57
	Other	9	32.14
Do the RCTs run by your CTU have HEAPs?	Always	8	29.63
	Sometimes	16	59.26
	Never	1	3.7
	Not required	0	0.00
	N/A	2	7.41
Does your CTU have a HEAP SOP or instructions in place?	Yes	10	37.04
	No	17	62.96
How often does your CTU write HEAPs for phase III trials?	Always	9	34.62
	sometimes	10	38.46
	never	2	7.69
	N/A	5	19.23
How often does your CTU write HEAPs for phase IV trials?	Always	7	25.93
	sometimes	9	33.33
	never	3	11.11
	N/A	8	29.63
How often does your CTU write HEAPs for pilot RCTs?	Always	6	22.22
	sometimes	9	33.33
	never	7	25.93
	N/A	5	18.52
How often does your CTU write HEAPs for full RCTs?	Always	16	57.14
	sometimes	5	17.86
	never	3	10.71
	N/A	4	14.29
How often does your CTU write HEAPs for commercially funded RCTs?	Always	2	7.41
	sometimes	3	11.11
	never	3	11.11
	N/A	19	70.37
How often does your CTU write HEAPs for publicly funded RCTs?	Always	12	42.86
	sometimes	9	32.14
	never	3	10.71
	N/A	4	14.29
Who is the intended audience of a HEAP? (can select >1)	Health economists	25	92.59
	statisticians	19	70.37
	chief investigator	23	85.19
	trials management group	20	74.07
	DMEC members	13	48.15
	TSC members	20	74.07
	funder-regulator	16	59.26
	other	2	7.41
	Before recruitment begins	4	15.38

When is a HEAP normally written and signed off?	before recruitment ends	6	23.08
	any time before the database is locked and final analysis begins	14	53.85
	other	2	7.69
Who is involved in drafting the HEAP? (can select >1)	Junior health economist	22	81.48
	senior health economist	25	92.59
	statistician	5	18.52
	chief investigator	14	51.85
	other	2	7.41
Who approves and signs off the HEAP? (can select >1)	Chief investigator	21	77.78
	statistician	6	22.22
	senior health economist-internal	20	74.07
	senior health economist- externa	6	22.22
	DMEC-TSC members	4	14.81
	other	7	25.93
If you do have a HEAP and/or HEAP SOPs would you be happy to share it with us for the purpose of facilitating this piece of research?	Yes	10	37.04
	no, we don't have a HEAP in our CTU	5	18.52
	no, we don't have a HEAP SOP in our CTU	10	37.04
	other reason	11	40.74

Appendix

Questions for the Health Economics Analysis Plans Survey

	Questions	**Possible answers**
Q1	Could you please state you name?	Open question
Q2	What is the name of the Clinical trials unit (CTU) you primarily work with?	Open question
Q3	Could you please describe your job title in the CTU?	Open question
Q4	Do you have a health economics team embedded within your CTU?	Yes/ No, but we collaborate with external health economics groups/ please state any other arrangements
Q5	Do the RCTs run by your CTU have HEAPs?	Always/sometimes/never/not required/non -applicable
Q6	Does your CTU have a HEAP SOP or instructions in place?	Yes/no
Q7	How often does your CTU write HEAPs for phase III trials?	Always/sometimes/never/non-applicable (our CTU does not undertake health economics on these trials)
Q8	How often does your CTU write HEAPs for phase IV trials?	Always/ sometimes/never/non-applicable (our CTU does not

		undertake health economics on these trials)
Q9	How often does your CTU write HEAPs for pilot RCTs?	Always/ sometimes/never/non-applicable (our CTU does not undertake health economics on these trials)
Q10	How often does your CTU write HEAPs for full RCTs?	Always/ sometimes/never/non-applicable (our CTU does not undertake health economics on these trials)
Q11	How often does your CTU write HEAPs for commercially funded RCTs?	Always/sometimes/ never/ non-applicable
Q12	How often does your CTU write HEAPs for publicly funded RCTs?	Always/sometimes/ never/ non-applicable
Q13	Who is the intended audience of a HEAP? (can select >1)	Health economists/ statisticians/ chief investigator/ trials management group/ DMEC members/ TSC members/ funder-regulator/ other (please specify)
Q14	When is a HEAP normally written and signed off?	Before recruitment begins/ before recruitment ends/ any time before the database is locked and final analysis begins/ other (please specify)
Q15	Who is involved in drafting the HEAP? (can select >1)	Junior health economist/ senior health economist/ statistician/ chief investigator/ other (please specify)
Q16	Who approves and signs off the HEAP? (can select >1)	Chief investigator/ statistician/ senior health economist-internal/ senior health economist- external/ DMEC-TSC members/ other (please specify)
Q17	If you do have a HEAP and/or HEAP SOPs would you be happy to share it with us for the purpose of facilitating this piece of research?	Yes/ no, we don't have a HEAP in our CTU/ no, we don't have a HEAP SOP in our CTU/ other reason (please specify)